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APPLICATION NUMBER:

761065Orig1s000

NON-CLINICAL REVIEW(S)

Tertiary Pharmacology/Toxicology Review

From: Timothy J. McGovern, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO

BLA: 761065 (Ibalizumab; TROGARZO)

Agency receipt date: May 3, 2017

Drug: Ibalizumab

Sponsor: TaiMed Biologics, Inc.

Indication: Treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen

Reviewing Division: Division of Antiviral Products

The pharmacology/toxicology reviewer, Team Leader and supervisor concluded that the nonclinical data support approval of ibalizumab for the indication listed above.

Ibalizumab is a CD4-directed humanized monoclonal antibody of immunoglobulin G (IgG) isotype 4 that is produced by recombinant DNA technology in murine myeloma non-secreting 0 NS0) cells. The recommended pharmacologic class for ibalizumab is “CD4-directed post-attachment HIV-1 inhibitor”. The drug is a first-in-class new molecular entity and was granted both orphan drug status and breakthrough therapy designation. It is proposed to be administered as an intravenous formulation and the proposed clinical regimen is a single loading dose of 2000 mg followed by 800 mg once every 2 weeks.

The nonclinical program primarily consists of repeat-dose toxicity studies in non-human primates up to 39-weeks in duration and tissue cross-reactivity studies in both normal human and rhesus monkey tissues. Non-human primates were appropriate based on similar binding affinity to humans and similar staining patterns in tissue cross-reactivity studies. The approximate half-life of ibalizumab in rhesus monkeys is 5.4 days. No adverse, drug-related findings were observed in any of the studies up to the highest doses tested; the exposure multiple at the NOAEL in the 39-week study was 13.9-fold relative to the proposed clinical dose. Anti-drug antibody formation was detected in all monkeys receiving ibalizumab starting around Day 14; observed clinical signs and effects of clinical pathology and kidney pathology were attributed to anti-drug antibody formation.

A carcinogenicity assessment and an enhanced pre/postnatal development study in cynomolgus monkeys will be submitted as post-marketing requirements based on previous agreements with the Division.

Conclusion:

I agree with the Division pharmacology/toxicology conclusion that ibalizumab can be approved from the nonclinical perspective. I have reviewed the proposed wording for the nonclinical sections of the product label and agree with the Division recommendations. The label will be updated upon submission of the enhanced pre/postnatal development study and carcinogenicity assessment.

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/s/

TIMOTHY J MCGOVERN
03/06/2018

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: 761065
Supporting document/s: 12 & 15
Applicant's letter date: May 3rd & 11th, 2017
CDER stamp date: May 3rd & 11th, 2017
Product: TROGARZO™ (Ibalizumab)
Indication: Treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing current antiretroviral therapy
Applicant: TaiMed Biologics, Inc.
Review Division: Division of Antiviral Products
Reviewer: David McMillan, Ph.D.
Supervisor/Team Leader: Christopher Ellis, Ph.D.
Division Director: Debra Birnkrant, M.D.
Project Manager: Christian Yoder, BSN, MPH

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	4
1.1	INTRODUCTION	4
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	4
1.3	RECOMMENDATIONS	4
2	DRUG INFORMATION	5
2.1	DRUG	5
2.2	RELEVANT INDs, NDAs, BLAs AND DMFs	5
2.3	DRUG FORMULATION	5
2.4	COMMENTS ON NOVEL EXCIPIENTS	5
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN	5
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	5
2.7	REGULATORY BACKGROUND	5
3	STUDIES SUBMITTED	6
3.1	STUDIES REVIEWED	6
3.2	STUDIES NOT REVIEWED	7
3.3	PREVIOUS REVIEWS REFERENCED	7
4	PHARMACOLOGY	7
4.1	PRIMARY PHARMACOLOGY	7
4.3	SAFETY PHARMACOLOGY	8
5	PHARMACOKINETICS/TOXICOKINETICS	8
6	GENERAL TOXICOLOGY	9
6.1	SINGLE-DOSE TOXICITY	9
6.2	REPEAT-DOSE TOXICITY	10
7	GENETIC TOXICOLOGY	16
8	CARCINOGENICITY	16
9	REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY	17
10	SPECIAL TOXICOLOGY STUDIES	17
11	INTEGRATED SUMMARY AND SAFETY EVALUATION	18

Table of Tables

Table 1: Ibalizumab drug formulation	5
Table 2: PK parameters from the single-dose monkey study (total mAb)	9
Table 3: PK parameters from the single-dose monkey study (monospecific mAb)	9
Table 4: Toxicokinetic parameters for the 9-month monkey study	16
Table 5: Ibalizumab safety margins	20

1 Executive Summary

1.1 Introduction

TaiMed Biologics, Inc., has submitted a biologic license application for ibalizumab, a CD4 post-attachment HIV-1 inhibitor for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing current antiretroviral therapy. Ibalizumab blocks HIV-1 infection of CD4⁺ T cells by interfering with the post-attachment steps required for cell-cell fusion and entry of HIV-1 into host cells. Ibalizumab is a first-in-class new molecular entity, was granted both orphan drug status and breakthrough therapy designation, and is intended to be marketed as an intravenous formulation. The proposed clinical regimen is a single loading dose of 2000 mg, administered intravenously, followed by 800 mg IV once every 2 weeks, in combination with other antiretroviral drugs. To support the nonclinical safety assessment of ibalizumab, the applicant submitted, in part, intravenous repeat-dose general toxicology studies in non-human primates up to 39 weeks in duration and tissue cross-reactivity studies in both normal human and rhesus monkey tissues. In addition, an enhanced pre/postnatal development study in cynomolgus monkeys is currently in progress and will be submitted as a post-marketing requirement.

1.2 Brief Discussion of Nonclinical Findings

Non-human primates were selected as the relevant species due to the similarity in binding affinity of ibalizumab to human and monkey CD4, and the similarity in binding patterns between rhesus monkey and human in the tissue cross-reactivity studies. Ibalizumab was not associated with any clinically-relevant adverse effects in the repeat-dose general toxicology studies in monkeys up to the highest doses tested. No clear effects on the immune system, including no drug-related effects on CD4⁺ T cell levels, immune cell phenotyping, lymphocyte proliferation, or cytokine production, were observed. Further, no effects on proliferation, activation, or apoptosis in human and monkey lymphocytes were observed *in vitro*.

1.3 Recommendations

1.3.1 Approvability

The nonclinical data submitted are sufficient to support licensure.

1.3.2 Additional Nonclinical Recommendations

As previously agreed, the applicant will be asked to submit the final study report for the enhanced pre/postnatal development study in cynomolgus monkeys as well as the carcinogenicity risk assessment as post-marketing requirements.

1.3.3 Labeling

Label is under review.

2 Drug Information

2.1 Drug

<u>Generic Name</u>	Ibalizumab
<u>Code Name</u>	TMB-355, TNX-355, Hu5A8, BG9169
<u>Chemical Name</u>	Humanized monoclonal antibody (IgG ₄ kappa) against CD4 receptor domain 2
<u>Molecular Weight</u>	~150 kDa
<u>Pharmacologic Class</u>	CD4 post-attachment HIV-1 inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

INDs 9776 and 108904.

2.3 Drug Formulation

The following table was excerpted and reformatted from the applicant's reports.

Table 1: Ibalizumab drug formulation

Ingredient	Function	Amount Per 1 mL Vial
Ibalizumab (cGMP)	Active Ingredient	150 mg
Sucrose (N.F.)	(b) (4)	(b) (4)
Sodium Chloride (USP)		
Polysorbate 80 (Ch.P.)		
L-Histidine (USP)		
(b) (4)		

2.4 Comments on Novel Excipients

No novel excipients are included in the ibalizumab drug product. All excipient exposures fall below maximum potencies listed for approved products in the FDA Inactive Ingredient Database.

2.5 Comments on Impurities/Degradants of Concern

No specific concerns have been identified.

2.6 Proposed Clinical Population and Dosing Regimen

A single loading dose of 2000 mg IV followed by 800 mg IV once every 2 weeks, in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing current antiretroviral therapy.

2.7 Regulatory Background

The intravenous formulation of ibalizumab was opened under IND 9776 in April 2001. The subcutaneous formulation was opened under IND 108904 in May 2010.

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacodynamics:

- 1) A humanized form of a CD4-specific monoclonal antibody exhibits decreased antigenicity and prolonged plasma half-life in rhesus monkeys while retaining its unique biological and antiviral properties (TMB-RD-R2017003)
- 2) *In vivo* administration to rhesus monkeys of a CD4-specific monoclonal antibody capable of blocking AIDS virus replication (TMB-RD-R2017009)
- 3) The binding affinity measurement of 5A8 human IgG4 against soluble CD4 (TMB-RD-R2017013)
- 4) Hu-5A8 IND pharmacology and toxicology information, volume 5 section 8 excerpt (S-0000)

Pharmacokinetics:

- 1) Bioanalytical and pharmacokinetics report of SBI study number 1652-181, a pharmacokinetics/pharmacodynamic comparison study of TNX-355 and related monoclonal antibodies administered as a single dose by intravenous injection to male cynomolgus monkeys (S-020/TXPK-1021)

Single & Repeat-Dose Toxicology:

- 1) A pilot pharmacokinetics and toxicology study of BG9169 following intravenous administration to rhesus monkeys (2-N98)
- 2) A pharmacokinetic and toxicology study of BG9169 following multidose intravenous administration to rhesus monkeys (2-P63)
- 3) Hu5A8: Multiple dose toxicity study in rhesus monkeys with a 10 week recovery period (575384)
- 4) A 9-month toxicity study of TNX-355 administered intravenously to cynomolgus monkeys, with a 3-month recovery period (MNA00001/TXPK-1023)
- 5) A 9-month toxicity study of TNX-355 administered intravenously to cynomolgus monkeys, with a 3-month recovery period: pharmacokinetic report (TMB-RD-R2017017)
- 6) A subcutaneous repeat dose toxicity and toxicokinetic study of TNX355 over a period of 15 days with a 30-day recovery period in cynomolgus monkeys (47803-10-432)

Special Toxicology Studies:

- 1) Cross-reactivity of Hu5A8 with normal human tissues (IM639)
- 2) Cross-reactivity of Hu5A8 with normal rhesus monkey tissues (IM640)
- 3) Immune response in chimpanzees to a single infusion of Hu5A8 (Fung & Gordon, 2001)
- 4) TNX-355: Measurement of TNX-355 concentration in the serum of cynomolgus monkeys from an antigenicity evaluation study (S-1052)
- 5) TNX-355: Measurement of anti-TNX-355 concentration in the serum of cynomolgus monkeys from an antigenicity evaluation study (S-1053)

3.2 Studies Not Reviewed

Studies considered irrelevant for the nonclinical safety assessment were not reviewed.

3.3 Previous Reviews Referenced

The nonclinical safety studies were reviewed by Drs. Christopher Ellis and David Essayan, and are summarized, as appropriate, in the following sections of this review.

Note: All tables in this review are excerpted from the applicant's reports.

4 Pharmacology

4.1 Primary Pharmacology

See virology review by Dr. Eric Donaldson for additional pharmacology information.

The binding affinity measurement of 5A8 human IgG4 against soluble CD4 (TMB-RD-R2017013)

The binding affinity of ibalizumab (Hu5A8) to soluble human CD4 was determined with a kinetic exclusion assay (KinExA®). Ibalizumab binds to soluble human CD4 with a $K_d = 82.2$ pM.

***In vivo* administration to rhesus monkeys of a CD4-specific monoclonal antibody capable of blocking AIDS virus replication (TMB-RD-R2017009)**

The binding affinity of Mu5A8, the murine progenitor of ibalizumab, to primary normal human and rhesus monkey CD4⁺ peripheral blood lymphocytes (PBLs) was determined by flow cytometry. Mu5A8 binds to CD4⁺ PBLs from both species with similar affinities ($EC_{50} = 0.8$ and 0.6 µg/mL for human and monkey PBLs, respectively). CD4⁺ T cell levels were also measured in rhesus monkeys following either a single dose of 3 mg/kg Mu5A8 or repeat doses of 3 mg/kg Mu5A8 once every 2 two days up to Day 6 (3 total doses). After a single dose of Mu5A8 in 2 animals, CD4⁺ T cells were confirmed by flow cytometry to be fully coated with Mu5A8 for 5 days post-dose. A transient increase in CD4⁺ cells also occurred 2 days post-dose and returned to baseline by Day 6, which corresponded to anti-Mu5A8 antibody formation in both animals starting around Day 6. Following repeat doses of Mu5A8, CD4⁺ T cell levels were increased by ~50% up to Day 9, which corresponds to Mu5A8 coating of CD4⁺ T cells in these animals. No difference in anti-tetanus antibody production, induced by tetanus toxoid, was observed relative to controls following repeat doses of Mu5A8, suggesting that Mu5A8 does not affect humoral immunity in this model.

A humanized form of a CD4-specific monoclonal antibody exhibits decreased antigenicity and prolonged plasma half-life in rhesus monkeys while retaining its unique biological and antiviral properties (TMB-RD-R2017003)

The binding affinities of ibalizumab (Hu5A8) and Mu5A8 to a human CD4⁺ cell line (Jurkat cells) and primary rhesus monkey PBLs were measured by flow cytometry. Both ibalizumab and Mu5A8 bind to both human and monkey cells with similar affinities ($EC_{50} = 10-25$ ng/mL and $2-20$ ng/mL for human and monkey cells, respectively). CD4⁺

T cell levels were also measured in rhesus monkeys following a single dose of ibalizumab (1, 3 and 30 mg/kg). A dose-dependent increase in the duration of CD4⁺ T cell coating with ibalizumab was observed up to Day 14 at the high dose. Transient increases in CD4⁺ T cell levels were also observed at all dose levels and returned to baseline by Day 14, and corresponded with ADA formation about 2 weeks post-dose in all treated animals. The half-lives of ibalizumab and Mu5A8 were calculated to be about 5.4 days and 28 hours, respectively.

Hu-5A8 IND pharmacology and toxicology information, volume 5 section 8 excerpt (S-0000)

The proliferation and apoptosis of primary human PBMCs and CD4⁺ PBLs were evaluated following *in vitro* incubation with either ibalizumab (Hu5A8) or Mu5A8. T cell proliferation induced by OKT3, an anti-CD3 antibody, was not affected by either Mu5A8 or ibalizumab for up to 48 hours at concentrations up to 50 µg/mL. Likewise, ibalizumab and Mu5A8 did not significantly affect tetanus toxoid-induced proliferation of human PBLs from tetanus toxoid-seropositive donors up to 6 days post-incubation at concentrations up to 10 µg/mL. Further, ibalizumab did not induce either apoptosis in human CD4⁺ PBLs (up to 50 µg/mL) or proliferation in primary human PBMCs (up to 20 µg/mL), up to 3 days post-treatment. Lastly, the activation and proliferation of PBMCs from naïve rhesus monkeys were evaluated following *in vitro* incubation with up to 10 µg/mL ibalizumab. PBMC proliferation was not significantly affected up to 6 days post-incubation. Likewise, no significant differences in expression of T cell activation markers CD25, CD69 or MHC class II were observed relative to controls up to 7 days post-incubation.

4.3 Safety Pharmacology

Dedicated safety pharmacology studies with ibalizumab have not been conducted. ECGs were recorded and evaluated in the 8-week and 39-week repeat-dose toxicology studies in non-human primates. No remarkable findings were observed.

5 Pharmacokinetics/Toxicokinetics

Study title: Bioanalytical and pharmacokinetics report of SBI study number 1652-181, a pharmacokinetics/pharmacodynamic comparison study of TNX-355 and related monoclonal antibodies administered as a single dose by intravenous injection to male cynomolgus monkeys (S-020/TXPK-1021)

Pharmacokinetics were evaluated in cynomolgus monkeys following administration of either ibalizumab (TNX-355), generated from two different cell lines (803.43-2 and H3) or one of three potential second-generation molecules (G4H-IgG4, G4D-IgG4 and MV1-IgG1). All groups received single intravenous doses of 10 mg/kg (4 males/group). As IgG4 antibodies can form bispecific molecules by undergoing exchange of IgG half molecules with other IgG4s *in vivo* (see Aalberse, et al., "IgG4 breaking the rules." *Immunology*. Jan 2002;105(1):9-19), pharmacokinetic parameters for both total antibody and monospecific antibody only were obtained for each molecule (**Tables 2 & 3**, respectively). Due to similarities in half-life and exposure, the sponsor concluded that none of the candidates were significantly improved over ibalizumab.

Table 2: PK parameters from the single-dose monkey study (total mAb)

Group No.	Test Article	C _{max} (µg/mL) ¹	AUC _{INF} (hr*µg/mL) ¹	t _{1/2} elim (hr)	V _z (mL/kg) ¹
1	TNX-355 803-43.2 cell line	379.6 ± 36.0	30606 ± 4163	59.9 ± 12.7	28.1 ± 3.8
2	TNX-355 H3 cell line	261.2 ± 21.9	23743 ± 3813	75.4 ± 26.7	44.8 ± 9.5
3	G4H-IgG4	297.5 ± 20.7	29994 ± 5374	83.7 ± 25.6	39.6 ± 4.6
4	G4D-IgG4	361.9 ± 23.5	32845 ± 2736	83.3 ± 12.3	36.4 ± 2.7
5	MV1-IgG1	350.1 ± 40.8	25164 ± 2886	67.2 ± 14.1	38.4 ± 5.5

¹ Group means significantly different by ANOVA (p<0.05)

Table 3: PK parameters from the single-dose monkey study (monospecific mAb)

Group No.	Test Article	C _{max} (µg/mL)	AUC _{INF} (hr*µg/mL) ¹	t _{1/2} elim (hr) ¹	T _{last} (hr) ¹	V _z (mL/kg)
1	TNX-355 803-43.2 cell line	373.9 ± 17.2	14725 ± 3916	32.9 ± 8.9	102 ± 50	32.3 ± 4.4
2	TNX-355 H3 cell line	320.3 ± 35.5	9179 ± 2760	19.3 ± 5.9	108 ± 72	30.4 ± 1.0
3	G4H-IgG4	337.0 ± 35.9	28781 ± 4754	75.5 ± 20.3	240 ± 0	37.4 ± 3.8
4	G4D-IgG4	376.2 ± 24.4	28588 ± 4286	72.3 ± 16.5	240 ± 0	36.2 ± 3.4
5	MV1-IgG1	359.2 ± 43.6	22710 ± 3705	56.3 ± 3.9	222 ± 36	36.4 ± 5.2

¹ Group means significantly different by ANOVA (p<0.05)

6 General Toxicology

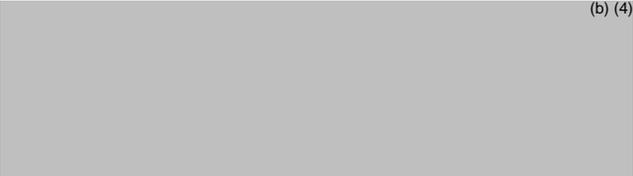
6.1 Single-Dose Toxicity

Study title: A pilot pharmacokinetics and toxicology study of BG9169 following intravenous administration to rhesus monkeys (2-N98)

Mortality, clinical exams, body weights, hematology, serum chemistry, urinalysis, immunogenicity, and immune cell phenotyping were performed or evaluated in rhesus monkeys following a single IV dose of 30 mg/kg ibalizumab (2/sex; no control group). Coating of CD4⁺ T cells with ibalizumab was observed up to 28 days post-dose. No adverse drug-related changes were observed.

6.2 Repeat-Dose Toxicity

Study title: A subcutaneous repeat dose toxicity and toxicokinetic study of TNX355 over a period of 15 days with a 30-day recovery period in cynomolgus monkeys

Study no.: 47803-10-432
Study report location: EDR
Conducting laboratory and location:  (b) (4)

Date of study initiation: May 31st, 2010
GLP compliance: Yes, with minor exceptions
QA statement: Yes
Drug, lot #, and % purity: TNX-355 (lot #1-NFF-0111, purity not provided)

Summary

Mortality, clinical exams, body weights, hematology, serum chemistry, local tolerance, gross pathology, organ weights, histopathology and drug serum concentrations were performed or evaluated in cynomolgus monkeys following once weekly subcutaneous injections of ibalizumab (2 or 20 mg/kg/dose; 2/sex/main group and 1/sex/recovery group). Animals were dosed on Days 1, 8 and 15 (3 total doses), and were euthanized on either Day 17 or 45. Each animal also served as its own control, having received drug and placebo in the right and left inner thighs, respectively. There were no unscheduled deaths. Minimal lymphoid hyperplasia of the right inguinal lymph nodes characterized by expanded germinal centers with increased cell density in paracortical areas was observed in 2 low-dose and 1 high-dose animals. Injection site reactions consisting of minimal to mild erythema in 1 high-dose male, and minimal to mild perivascular infiltrates in the dermis and subcutis composed of neutrophils, macrophages, lymphocytes and eosinophils in 1 low-dose female were also observed (erythema was also present at control sites in 2 animals). Potassium (14-28%) and calcium (5-7%) were decreased at both dose levels relative to pre-dose values on Day 17. ALP was increased 26% relative to pre-dose values in low-dose males on Day 17. Bilateral multifocal discoloration of the thymus was present in 1 high-dose animal at Day 45. All findings were drug-related, though were considered non-adverse.

NOAEL = 20 mg/kg/week.

Study title: A pharmacokinetic and toxicology study of BG9169 following multidose intravenous administration to rhesus monkeys

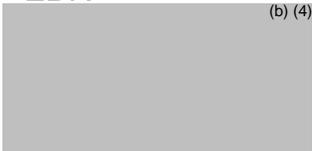
Study no.: 2-P63
Study report location: EDR
Conducting laboratory and location:  (b) (4)
Date of study initiation: October 7th, 1993
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: BG9169 (lot #H3-5A8 2927, purity = 97%)

Summary

Mortality, clinical exams, body weights, hematology, serum chemistry, urinalysis, gross pathology, organ weights, histopathology, TNF- α serum levels, and lymphocyte phenotyping and proliferation were performed or evaluated in rhesus monkeys following IV doses of either vehicle (sterile saline for injection; 2/sex) or ibalizumab (1 or 10 mg/kg/dose; 2/sex/primary group and 1/sex/recovery group). Animals were treated once every three days (Days 1, 4, 7, 10 and 13), and were euthanized on either Day 14 or 56. There were no unscheduled deaths, and no changes in CD4⁺ T cell levels or other immune endpoints. The high dose was likely reaching maximum receptor occupancy based on measurement of ibalizumab-coated CD4⁺ T cells. No adverse, drug-related changes were observed.

NOAEL = 10 mg/kg/dose.

Study title: Hu5A8: Multiple dose toxicity study in rhesus monkeys with a 10 week recovery period

Study no.: 575384
Study report location: EDR
Conducting laboratory and location:  (b) (4)
Date of study initiation: August 9th, 2000
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Hu5A8 (lot #T662-61, purity not provided)

Summary

Mortality, clinical exams, body weights, food consumption, ophthalmic exams, electrocardiography, hematology, serum chemistry, urinalysis, gross pathology, organ weights, histopathology, immunohistochemistry for CD3/4/8 and IgG/M/D, immune cell phenotyping, T cell proliferation, immunogenicity, and toxicokinetics were performed or evaluated in rhesus monkeys following IV doses of either vehicle (3/sex) or ibalizumab

(5 or 25 mg/kg/dose; 3/sex/primary group and 2/sex/recovery group). Animals were treated once weekly from Day 1 to 50 (8 total doses), and were euthanized on either Day 56 or 126. There were no unscheduled deaths, and no changes in CD4⁺ cell levels or other immune endpoints. The high dose was likely reaching maximum receptor occupancy based on measurement of ibalizumab-coated CD4⁺ T cells. Immunogenicity was observed starting around Day 14, and was present in all treated animals at Day 50, and in 6 of 8 animals at Day 121. Anti-drug antibody levels were generally higher and lasted longer in the low-dose group. Due to high immunogenicity and low drug exposures, particularly at the low dose, Day 50 toxicokinetic parameters could not reliably be obtained. No adverse, drug-related changes were observed.

NOAEL = 25 mg/kg/week ($AUC_{0-t} = 1253.46 \mu\text{g}\cdot\text{day/mL}$, $C_{\text{max}} = 432.57 \mu\text{g/mL}$ at Day 1).

Study title: A 9-month toxicity study of TNX-355 administered intravenously to cynomolgus monkeys, with a 3-month recovery period

Study no.: MNA00001/TXPK-1023
Study report location: EDR
Conducting laboratory and location:  (b) (4)

Date of study initiation: May 19th, 2004
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: TNX-355 (lot #T1014-171, purity not provided)

Key Study Findings

NOAEL = 50 mg/kg/week ($AUC = 12400.06 \mu\text{g}\cdot\text{day/mL}$, $C_{\text{max}} = 2735.45 \mu\text{g/mL}$ at Day 260). Several treated animals were euthanized on Days 193 and 194 due to low drug exposure/immunogenicity. All significant toxicities (clinical signs, serum chemistry, necropsy findings) were attributed to anti-drug antibody formation. No adverse drug-related findings were observed.

Methods

Doses: 0, 25 & 50 mg/kg/dose
Frequency of dosing: Once weekly
Route of administration: Intravenous (bolus)
Dose volume: 1-2 mL/kg
Formulation/Vehicle: 10 mM histidine, (b) (4) mg/mL sucrose & (b) (4) % polysorbate 80, pH = (b) (4)
Species/Strain: Cynomolgus monkeys
Number/Sex/Group: 4/sex/main study group, 2/sex/recovery group
Age: Males = 2.3 to 4.9 years, Females = 2.4 to 4.9 years
Weight: Males = 2.6 to 3.2 kg, Females = 2.1 to 2.9 kg
Satellite groups: None
Unique study design: None
Deviation from study protocol: None which affected interpretation of the study

Observations and Results

Mortality

Morbidity and mortality were assessed twice daily. Seven low-dose and 1 high-dose animals, along with two control animals for comparison, were euthanized prematurely on Days 193 and 194 due to immunogenicity and extremely low drug exposures beyond Day 29 at the low dose, and Day 57 at the high dose.

Clinical Signs

Cage-side observations were performed twice daily. Detailed exams were performed pretreatment and at 2, 6 and 9 months. The following were observed:

- Drowsiness, incoordination/ataxia and excess salivation in 1 low-dose and 1 high-dose females during/immediately post-dose beginning at Day 43. Excess salivation was also present in a second low-dose female. The high-dose female also passed out/collapsed on Days 43 and 78. All three animals all exhibited high immunogenicity and the lowest drug serum concentrations of all females (no exposure beyond Day 29/57).
- Reddened area with multiple masses, yellow discharge and ulcerations on left thigh in one high-dose female starting on Day 272.
- Watery stool starting at Day 76 along with decreased activity, weakness and very thin body on Day 259 in one low-dose female.

Drowsiness, incoordination, ataxia, and passing out/collapse may be attributed to immunogenicity. Findings on the left thigh were likely due to KLH, which was administered at this site. Excess salivation may be drug-related, but was considered non-adverse. All other findings may be incidental and unrelated to treatment.

Body Weights

Body weights were measured once weekly. There were no drug-related changes.

Food Consumption

Food consumption was measured once daily. There were no drug-related changes.

Ophthalmoscopy

Ophthalmoscopy was performed pretreatment and at 2, 6 and 9 months. There were no drug-related changes.

Electrocardiography

ECGs were recorded pretreatment and at 2, 6 and 9 months, and were analyzed qualitatively. There were no drug-related changes.

Hematology

Blood samples were collected pretreatment, at 2, 6 and 9 months, and after recovery. Immune cell phenotyping was also performed by flow cytometry at the same time points. The following were observed:

- Decreased basophils (92%) in high-dose males prior to treatment at Day 57. This finding was not statistically significant, was not present in females, and was not observed at any other time point.
- Band neutrophils present in 2 high-dose males (one at Day 57 and one at Day 182), and in 2 low-dose females (one at Day 182 and one at Day 260). Also present pretreatment in 1 control female.
- Increased lymphocytes (46%) in high-dose animals at Day 267 as measured by flow cytometry. Increased CD3⁺/CD8⁺ T cells relative to controls (76%) at the high dose at Day 267. Increased CD3⁺/CD4⁺ T cells relative to pre-dose (32%) in high-dose males at Day 57. No differences were observed in the recovery animals. No decreases in CD4⁺ T cells were observed.

The decrease in basophils was considered incidental and unrelated to treatment. All other findings may be drug-related, but were considered non-adverse.

Clinical Chemistry

Blood samples were collected pretreatment, at 2, 6 and 9 months, and after recovery. Decreased albumin was observed in 1 low-dose male and 1 high-dose female (36% and 49%, respectively) at Day 182. Both animals exhibited high immunogenicity, and the female was euthanized on Day 194 due to low exposure. Exposure in the male animal was the lowest of all males in this study. Both animals also had minimal multifocal glomerulopathies in the kidneys (see Histopathology section).

Coagulation

Blood samples were collected pretreatment, at 2, 6 and 9 months, and after recovery. There were no drug-related changes.

Gross Pathology

Gross pathology was assessed at the times of necropsy on Days 193/194, 270 and 365. There were no drug-related changes.

Organ Weights

Organ weights were measured at the times of necropsy on Days 193/194, 270 and 365. The following were observed:

- Decreased spleen weight (45%) in 1 high-dose female at Day 193/194. This female also had clinical signs and was euthanized due to immunogenicity.

- Decreased thymus weight (~44%) relative to body weight in the high-dose animals. Not present in recovery.

Histopathology

Adequate Battery Yes

Peer Review No

Histological Findings Histopathology was assessed at the times of necropsy on Days 193/194, 270 and 365. Euthanasia on Day 193/194 were performed due to low exposure/immunogenicity. The following were observed:

- Minimal multifocal glomerulopathy of mesangium, and increased mesangial matrix in glomeruli in kidneys, in 2 low-dose and 1 high-dose females, and 1 low-dose male. The low-dose male and high-dose female also had decreased serum albumin levels at Day 182. All four animals were euthanized on Days 193/194, and the sponsor attributed these findings to immune complex formation. Not present at Day 270 (in animals with good exposure), or after recovery.
- Minimal multifocal mononuclear cell infiltrate in meninges in 1 low-dose male and 1 low-dose female at Day 193/194, and 2 high-dose males and 1 high-dose female at Day 270. Also in 1 high-dose and 1 control males after recovery.
- Minimal multifocal hemorrhage in thymus in 1 low-dose male and 1 low-dose female on Day 193/194. Also present in 1 low-dose and 1 high-dose males, and 2 high-dose females, at Day 270. Also present in 1 low-dose female, 1 high-dose male, and one control female after recovery.
- Minimal to mild thymic involution in 1 low-dose female at Day 193/194. Also present in 2 low-dose and 2 high dose males, and 1 low-dose and 2 high-dose females at Day 270 (also 2 male controls). Also present in 1 low-dose and 1 mid-dose males, and 1 male and 1 female controls, after recovery.
- Moderate bilateral size increase with mild multifocal lipid granulomatous inflammation of iliac and inguinal lymph nodes in 1 high-dose recovery female.

The kidney findings were attributed to immune complex formation. It is unclear whether the meninges, thymus and lymph node findings were drug-related or incidental.

Immunotoxicity

The immune response to KLH challenge was measured on Days 38, 52, 241, 255, 330 and 344. The following were observed:

- Increased IgM (23-26%) at Days 48 and 59 in high-dose animals. May be due to a slight increase in CD4⁺ T cell levels (see Hematology section).
- Increased IgG in 1 high-dose male throughout the study (also increased in one control female starting at Day 241).

Immunogenicity

Blood samples were collected pretreatment and on Days 14, 28, 57, 182, 267 and 364. Anti-drug antibody formation was observed in 10 low-dose and 7 high-dose animals. Of these, 7 low-dose and 1 high-dose animals had little to no drug exposure by Day 57 and were euthanized on Days 193/194.

Toxicokinetics

Blood samples were collected on Days 1, 57 and 260 pretreatment and 0.25, 4, 24, 48 and 72 hours post-dose, on Days 29, 92, 120, 148, 183, 211 and 239 pretreatment and 1 hour post-dose, and on Days 8, 64, 99 and 267 pretreatment only. Low drug exposures were observed in 7 low-dose and 1 high-dose animals due to immunogenicity. Of the 7 low-dose animals, three had no exposure beyond Day 29. Likewise, no exposure was observed in the single high-dose animal beyond Day 57. These eight animals were euthanized on Day 193/194, and the serum concentrations from these animals after Day 29 were excluded from the toxicokinetic analysis. Toxicokinetic parameters for Days 1, 57 and 260 are presented in **Table 4**.

Table 4: Toxicokinetic parameters for the 9-month monkey study

Dose (mg/kg)	Day	T _{max} (Day)	C _{max} (µg/mL)	AUC (day*µg/mL)	T _{1/2} * (Day)	V _d * (mL/kg)	Cl* (mL*kg/day)
25	1	0.02 ± 0.05	763.37 ± 141.44	2093.75 ± 412.49	4.80 ± 1.58	52.41 ± 8.63	8.37 ± 2.88
	57	0.07 ± 0.09	1350.00 ± 196.89	5058.71 ± 2125.71	5.97 ± 3.69	19.31 ± 4.00	5.98 ± 8.16
	260	0.11 ± 0.09	1494.80 ± 49.73	6687.99 ± 1125.82	8.19 ± 3.40	19.35 ± 1.85	1.89 ± 0.89
50	1	0.01 ± 0.00	1677.50 ± 479.93	5218.19 ± 1995.97	5.61 ± 2.23	47.65 ± 12.75	6.93 ± 3.58
	57	0.25 ± 0.59	3603.18 ± 1753.30	14652.99 ± 5851.13	7.53 ± 2.42	20.58 ± 7.24	1.95 ± 0.59
	260	0.04 ± 0.06	2735.45 ± 540.25	12400.06 ± 2950.80	10.68 ± 3.03	23.47 ± 5.81	1.73 ± 1.00

* Parameters that require the assumption of linearity

Dosing Solution Analysis

All stability criteria for the drug and placebo were met.

7 Genetic Toxicology

Genotoxicology studies with ibalizumab were not needed in accordance with ICH S6.

8 Carcinogenicity

Carcinogenicity studies with ibalizumab have not been conducted. A carcinogenicity risk assessment will be submitted as a post-marketing requirement.

9 Reproductive and Developmental Toxicology

Fertility and early embryonic development and embryo-fetal development studies with ibalizumab have not been conducted. An enhanced pre/postnatal development study in cynomolgus monkeys is in progress and will be submitted as a post-marketing requirement.

10 Special Toxicology Studies

Study title: Cross-reactivity of Hu5A8 with normal human tissues (IM639)

The potential cross-reactivity of ibalizumab (Hu5A8) was detected in normal human tissues (3 donors per tissue). Positive (normal human lymph node cryosections) and negative controls (normal human cerebellum cryosections, human IgG4 kappa isotype control) produced appropriate responses. Moderate to intense staining was observed in the lymphoid tissues (lymph node, spleen, thymus and tonsil), and in lymphocytes in the adrenal and mammary glands, large and small intestines, esophagus, liver, lung, skin, thyroid, ureter and cervix. All staining was consistent with CD4 expression, and no significant background or off-target staining was observed.

Study title: Cross-reactivity of Hu5A8 with normal rhesus monkey tissues (IM640)

The potential cross-reactivity of ibalizumab (Hu5A8) was detected in normal rhesus monkey tissues (2 donors per tissue). Positive (normal human lymph node cryosections) and negative controls (normal human cerebellum cryosections, human IgG4 isotype control) produced appropriate responses. Weak to strong staining was observed in the lymphoid tissues (lymph node, spleen, thymus and tonsil), and in lymphocytes in the large and small intestines, esophagus, kidney, lung, placenta and bladder. All staining was consistent with CD4 expression, and no significant background or off-target staining was observed. Due to the similarity in binding patterns between rhesus monkey and human (study IM639), the rhesus monkey was considered an appropriate species for use in the general toxicology studies.

Study title: Immune response in chimpanzees to a single infusion of Hu5A8

Immunogenicity, hematology, serum chemistry, CD4⁺ and CD8⁺ T cell levels, and drug serum concentrations were evaluated in three chimpanzees following a single IV dose of 20 mg/kg ibalizumab (Hu5A8). Ibalizumab serum levels peaked at about 300 µg/mL 30 minutes post-dose and were undetectable by Day 15. Anti-drug antibody formation was not detected up to 42 days post-dose, and no changes relative to pre-dose values were observed in all other parameters evaluated. Ibalizumab was considered non-immunogenic in chimpanzees following a single IV dose.

Study title: Measurement of TNX-355 and anti-TNX-355 concentrations in the serum of cynomolgus monkeys from an antigenicity evaluation study (S-1052 & S-1053)

Immunogenicity and serum drug concentrations were evaluated in cynomolgus monkeys (3/group) following IV doses of ibalizumab (TNX-355). Group 1 and 2 animals received initial doses of either placebo or 10 mg/kg ibalizumab, respectively, on Day 1.

All animals received challenge doses of 50 mg/kg ibalizumab on Days 21 and 28. Anti-drug antibodies were detected in all Group 2 animals at Days 21 and 38, and at very low levels in one Group 1 animal at Day 38. Serum drug concentrations in Group 1 peaked on Day 28 and dropped about 3-fold by Day 38 (1873 to 587 µg/mL), while those in Group 2 peaked on Day 21 post-dose (931 µg/mL) and were undetectable by Day 35. The decreased serum concentrations in Group 2 relative to Group 1 were attributed to heightened immunogenicity in these animals.

11 Integrated Summary and Safety Evaluation

Biologic license application 761065 was submitted in support of ibalizumab, a CD4 post-attachment HIV-1 inhibitor for the treatment of HIV-1 infection in treatment-experienced, HIV-positive adults with multi-class resistance and limited treatment options. Ibalizumab blocks HIV-1 infection of CD4⁺ T cells by interfering with the post-attachment steps required for cell-cell fusion and entry of HIV-1 into host cells. Ibalizumab is a first-in-class new molecular entity, was granted both orphan drug status and breakthrough therapy designation, and is intended to be marketed as an intravenous formulation. The proposed clinical regimen is a single loading dose of 2000 mg, administered intravenously, followed by 800 mg IV once every 2 weeks, in combination with other antiretroviral drugs.

Pharmacology/Pharmacokinetics:

Ibalizumab binds to soluble human CD4 with a K_d of 82.2 pM, and both ibalizumab and its murine precursor, Mu5A8, bind to both human and monkey CD4⁺ T cells with similar affinities. The half-lives of ibalizumab and Mu5A8 in rhesus monkeys are approximately 5.4 days and 28 hours, respectively.

Safety Pharmacology:

ECGs were recorded and evaluated in the 8-week and 39-week repeat-dose toxicology studies in non-human primates. No remarkable findings were observed.

Immunotoxicology:

No clear effects on the immune system were observed in the nonclinical safety studies. The immune response to KLH challenge was evaluated as part of the pivotal, 39-week study in cynomolgus monkeys. No adverse findings were observed. In addition, there were no changes in CD4⁺ T cell levels or other immune endpoints (immune cell phenotyping, T cell proliferation, immunohistochemistry for CD3/4/8 and IgG/M/D in lymphoid tissues, or cytokine production) in the repeat-dose toxicology studies.

No differences in activation, as measured by expression of CD25, CD69 and MHC class II, or in proliferation were observed in naïve rhesus monkey PBMCs *in vitro* for up to 7 days post-treatment with ibalizumab. In addition, ibalizumab and Mu5A8 did not affect OKT3- or tetanus toxoid-induced proliferation of human PBLs for up to 6 days post-treatment, and ibalizumab did not induce either apoptosis or proliferation in primary human CD4⁺ PBLs or PBMCs for up to 3 days post-treatment.

Following a single dose of 3 mg/kg Mu5A8 in rhesus monkeys, transient increases in CD4⁺ T cell levels and coating of CD4⁺ T cells with Mu5A8 were observed which returned to baseline by Days 5-6. Anti-Mu5A8 antibody production was observed in these animals starting around Day 6. Similarly, in rhesus monkeys treated with three doses of 3 mg/kg Mu5A8 (once every two days), increased CD4⁺ T cell levels up to ~50%, and Mu5A8 coating of CD4⁺ T cells, were observed up to Day 9. No difference in anti-tetanus antibody production, induced by tetanus toxoid, was observed relative to controls following repeat doses of Mu5A8, suggesting that Mu5A8 does not affect humoral immunity in this model. As with Mu5A8, transient increases in CD4⁺ T cell levels and coating of CD4⁺ T cells were observed in rhesus monkeys following a single dose of ibalizumab (1, 3 and 30 mg/kg), which returned to baseline by Day 14. Anti-ibalizumab antibody formation was also detected in these animals about 2-weeks post-dose in all treated animals. No decreases in CD4⁺ T cells were observed.

Tissue Cross-Reactivity Studies:

All staining with ibalizumab in both human and monkey tissues was consistent with CD4 expression.

Repeat-Dose Toxicology:

Non-human primates were selected as the appropriate species for the general toxicology studies due to the similarity in binding affinity of ibalizumab for both human and monkey CD4, as well as the similarity in staining patterns in human and monkey tissues in the tissue cross-reactivity studies. Ibalizumab does not recognize CD4 in other species. General repeat-dose toxicology evaluations consisted of intravenous studies up to 39 weeks duration in monkeys. One subcutaneous study of 15 days duration was also conducted in monkeys. No adverse, drug-related findings were observed in any of the studies up to the highest doses tested. The exposure multiple at the NOAEL in the 39-week study was 13.9-fold relative to the proposed clinical dose. Anti-drug antibody formation was detected in all monkeys receiving intravenous ibalizumab starting around Day 14, and persisted in most animals throughout recovery. In the pivotal 39-week study, no drug exposure was observed in 7 low-dose and 1 high-dose animals at Day 57 due to high immunogenicity. These animals also exhibited clinical signs (drowsiness, incoordination/ataxia, and passing out/collapse), decreased serum albumin, and histopathology findings in the kidney (minimal multifocal glomerulopathy of mesangium, and increased mesangial matrix in glomeruli), all of which were attributed to anti-drug antibody formation, and were euthanized prematurely on Days 193-194.

Genotoxicology and Carcinogenicity:

Genotoxicology and carcinogenicity studies with ibalizumab have not been conducted. A carcinogenicity risk assessment will be submitted as a post-marketing requirement.

Reproductive and Developmental Toxicology:

Fertility and early embryonic development and embryo-fetal development studies with ibalizumab have not been conducted. An enhanced pre/postnatal development

study in cynomolgus monkeys is in progress and will be submitted as a post-marketing requirement.

Exposure Margins:

The exposure margins for ibalizumab are presented in **Table 5**.

Table 5: Ibalizumab safety margins

Study	NOAEL (mg/kg/dose)	Adverse Toxicities Observed	Nonclinical AUC ($\mu\text{g}\cdot\text{day}/\text{mL}$)	Exposure Multiple ^a
15-day SC	20	None	No TK data	N/A
2-week IV	10	None	No TK data	N/A
8-week IV	25 ^b	None	1253.46	1.4
9-month IV	50 ^c	None	12400.06	13.9

^a Based on predicted exposures in patients receiving a loading dose of 2000 mg ibalizumab followed by 800 mg q2wk from Week 2 to Week 24 ($\text{AUC}_{22-24\text{weeks}} = 895 \mu\text{g}\cdot\text{day}/\text{mL}$)

^b Day 1 data

^c Day 260 data

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/s/

DAVID H MCMILLAN
09/28/2017

CHRISTOPHER E ELLIS
09/28/2017

HANAN N GHANTOUS
09/29/2017

I agree with Dr. McMillan that the nonclinical data submitted are sufficient to support licensure of Ibalizumab.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 761065

Applicant: TaiMed Biologics

Stamp Date: May 3rd, 2017

Drug Name: Ibalizumab (Trogarzo) BLA Type: Original NME

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		A carcinogenicity assessment will be submitted as a post-marketing requirement. An enhanced pre-/postnatal development (ePPND) study is in progress and will be submitted as a post-marketing requirement.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		Appropriateness of content will be determined upon review and discussed at labeling meetings.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Not applicable.

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/s/

DAVID H MCMILLAN
06/27/2017

CHRISTOPHER E ELLIS
06/27/2017